Quantitative Morphology: Volumes, Shapes and Voxel-Based Measures

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December 7, 2005

Abstract

Most of the approaches dedicated to automatic morphometry rely on a point-by-point strategy based on warping each brain towards a reference coordinate system. The coordinate system is three dimensional for the comparison of the local densities of grey and white matter (voxel-based morphometry), or two dimensional (spherical) for the comparison of cortical thickness. A more intuitive alternative approach is based on Regions of Interest defined either maually or authomatically. The volumes and shapes of these ROIs (for insatnce sulci and gyri) can be compared across subjects. This talk will give an overview of these different strategies.

1 Introduction

Advances in neuroimaging have led to an increasing recognition that certain neuroanatomical structures may be preferentially modified by particular cognitive skills or diseases. For cognitive studies, this point of view relies on the supposition that specialized or preferred behaviour is associated with a commensurately greater allocation of neural circuitry in corresponding brain centers. For neurodegenerative disorders, the differential patterns of atrophy is supposed to reflect the clinical phenomenology [1]. This recognition has mainly resulted from the recent design of automated morphometric methods, which have empowered large-scale population studies [44, 2]. Therefore, brain morphometry is now one of the basic brain mapping tools at the same level as the various functional imaging modalities.

For most of the approaches, the automatic analysis relies on warping each brain towards a reference coordinate system, which plays the same role as the latitude and longitude system for localization of points on the Earth's surface [41, 19, 20, 46, 18, 28] (cf Fig 1, 2 and 3). The coordinate system is three dimensional for the comparison of the local densities of grey and white matter (voxel-based morphometry, VBM [2] "http://www.fil.ion.ucl.ac.uk/spm/"), or two dimensional (spherical) for the comparison of cortical thickness [17, 28] ("http://surfer.nmr.mgh.harvard.edu/"). Each new brain is endowed with one of these coordinate systems through **iconic spatial normalization**, namely a deformation matching as far as possible the new brain macroscopic anatomy as revealed by magnetic resonance imaging (MRI) with a template

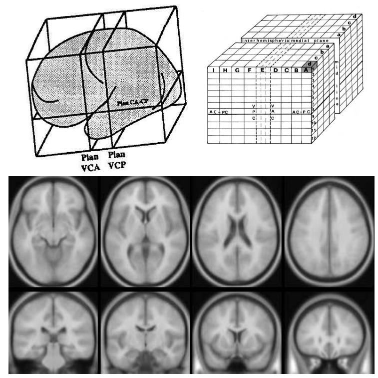

Figure 1: The 3D proportional coordinate system, based on a few landmarks, was introduced for neurosurgical purpose [41]. The modern approach is based on linear or nonlinear registration with a template made up of the average of a large number of brains [13, 20]. The most common template is based on 305 brains manually aligned in the Montreal Neurological Institute [16].

anatomy [13, 20, 18, 25]. The simplest approaches rely on affine transformations only, while modern registration techniques can now provide complex warpings relying on a large number of degrees of freedom, that are supposed to improve the normalization [22, 38, 7]. Nonlinear warping can be the basis for deformation-based morphometry, a sibling of the tissue density morphometries which is also coordinate-oriented [9, 36, 37].

The iconic spatial normalization paradigm, originally introduced to overcome the poor statistics of positron emission tomography (PET) data [19], has made a tremendous impact on brain mapping strategies [31]. The coordinate-based approach, indeed, is very versatile since any dataset can be compared simply on a point by point basis. A disturbing fact, however, is that a number of different normalization algorithms are used throughout the world, each one potentially leading to different normalization results [14, 24]. Even SPM software proposes a lot of alternatives related to the size of the warping function basis or to the choice of the template [20]. This observation means that what is called spatial normalization is far to be clear simply because nobody really knows the gold standard of brain matching. Furthermore, nobody knows today to which extent matching two different brains with a continuous deformation makes sense from a neuroscience point of view.

The part of the brain leading to the main difficulties is the cortex, because the large variability of the folding patterns prevents the warping from attempting a perfect gyral matching across subjects [32, 4, 24]. Therefore, it seems rather difficult to perform reliable coordinate-based morphometric studies without either spatially blurring the data [2] or involving hundreds of subjects [47, 21]. A number of teams try to overcome current difficulties via more sophisticated iconic normalization procedures [43]. A significant improvement, for instance, consists in warping inflated cortical surfaces according to depth or curvature features, which simplifies the matching of the major sulci [18]. In our opinion, however, without a better understanding of the inter-in-

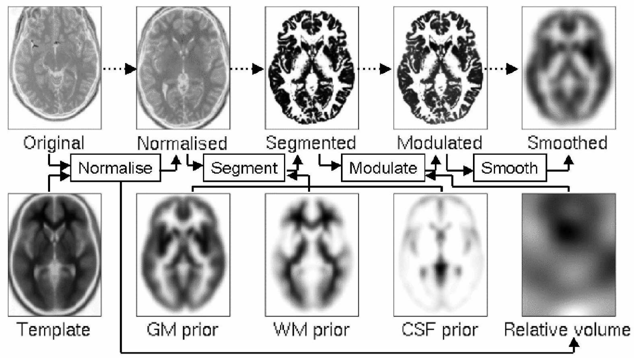

Figure 2: A rapid overview of VBM approach (from J. Ashburner [2]): each brain is spatially normalized first. Prior knowledge is then used to drive classification of the normalized image into three types of tissues. A correction is applied to account for modification of the amount of tissues induced by nonlinear warping (modulation). The resulting images are smoothed and compared across subjects on a voxel by voxel basis.

dividual variability of the cortical folding patterns, the risk is the drift toward pure morphing techniques without consistent architectural justification. Spatial normalization, indeed, should try to match as far as possible the architectural parcellations of the cortical sheet. Unfortunately, while some major sulci are usually considered as good indicators of architectonic or functional transitions, few people postulate that this property can be extrapolated to all cortical folds [48, 34]. Anyway, the approaches imposing some sulcus-based constraints in the warping procedures [42, 11, 8, 23] seem more reasonable than blind morphing procedures only driven by image grey levels or surface curvature, even if some progress has to be made with regard to the automatic identification and the choice of the sulci to be matched.

An alternative to the coordinate-based point of view is the classical ROI-based strategy. The structures of interest are segmented manually or automatically and various morphometric parameters related to their shapes are compared across subject. For the cortex, this alternative can rely on pattern recognition systems identifying the sulci or the gyri [35, 6, 30, 29]. It should be noted that this kind of ROI-based strategy is data-driven. Therefore, the ROIs actually fit individual anatomy. In contrast, the ROI-based strategy which warps a segmentation of the template brain [12, 10] suffers from the weakness of iconic normalization with regard to sulco/gyral patterns.

A first key point of the ROI-based strategy is that the combination of measurements gathering a subset of voxels increases the statistical power. This combination of measurements can simply rely on some averaging process, for instance through the computation of the mean thickness in a surface patch; but the ROI definition leads also to the emergence of new morphometric opportunities provided by various ROI-shape features. For instance the number and the types of interruptions of the major sulci, or the fact that two major sulci are connected or not, have never been correlated to cognitive features. The burried gyri leading to these interruptions [5], however, may be deeply correlated with the functional organization. This has been shown in the case of Broca's

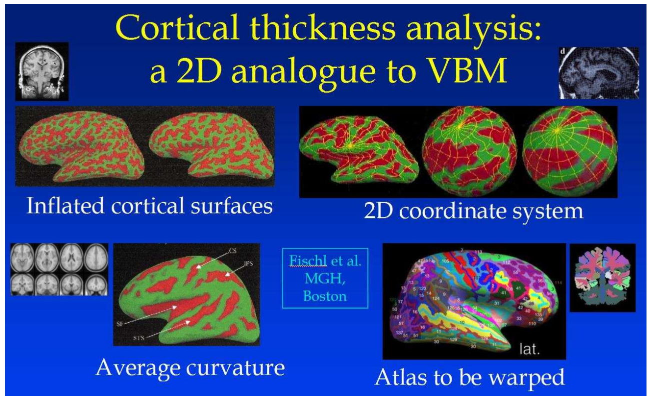

Figure 3: Cortical thickness analysis [18, 17, 28] is a new morphometric approach that can be viewed as a 2D analogue to VBM. Cortical thickness is compared across subjects on a point by point basis after alignment of the cortical surfaces with a spherical coordinate system.

"pli de passage moyen", namely the gyrus burried in the central sulcus [33, 50, 3]. Some other interesting morphometric features are the depth and the surface of a given sulcus, which may give some clues about the development of the surrounding functional areas, because of the tensegrity principle: the idea that the folding reaches its final pattern via stabilization of the sum of tensions and compressions stemming from the different parts of the cortex (axone bundles, cortical mantle, etc...) [34, 45]. Hence, a second key point of the object-based strategy is the possibility to compare the various instances of the same anatomical entity without requiring a point-to-point warping, which may not exist. We do not claim such an approach provides miraculous solutions to the difficulties induced by the variability of the cortex folding patterns, but only a new window to compare the cortex shapes. The relevance of a sulcus-based parcellation system is supposed to stem from the complex links with the cortex architectony mentioned above.

The increase in statistical power provided by the classical ROI-based strategy leads to a loss of localization power. This is good reason why this approach should be associated with some more sophisticated local analysis. For instance, each sulcus can be endowed with a 2D coordinate system in order to perform either local cortical thickness analysis or statistical shape modeling [27, 15, 40]. This structure-based local coordinate system strategy, unfortunately, does not deal nicely with the topological variability of the sulci. Therefore, it may be easier to apply the local coordinate systems to the gyri, which are usually non interrupted.

Considering the complexity of adapting a coordinate system to each cortical structure, an attractive alternative may consist in mixing warping and sulcus recognition in a hierarchical manner. A first affine registration may be used to constraint the recognition of the major sulci, following the strategy of our artificial neuroanatomist [35]. Then a non linear warping aligning these major sulci would result in a refined normalization [8], this new coordinate system being used to constraint the recognition of more variable sulci. This process could be iterated as long as new sulcal landmarks can be

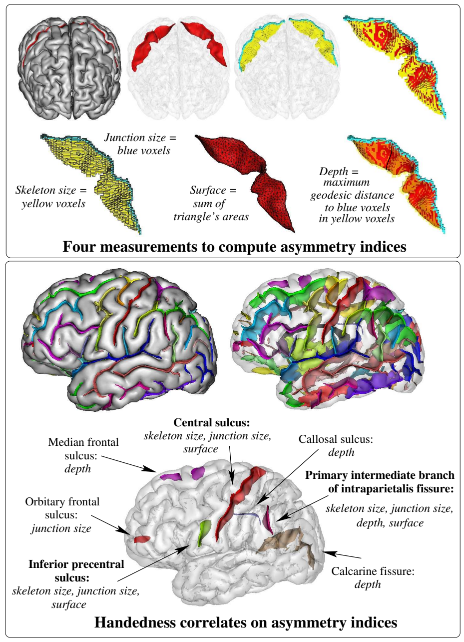

Figure 4: **Top:** Each sulcus (here the central sulcus) is extracted in each hemisphere as a skeleton subset. In this figure, yellow voxels denote the main part of this subset, while cyan voxels correspond to the junction with the brain hull. This set of voxels is then meshed in order to have access to smooth 3D rendering of the sulcus shape (red). Several morphometric measurements are inferred from the two types of representations. **Bottom:** 58 sulcus have been identified in each of 142 brains. For each sulcus, an index of asymmetry is computed for each of the morphometric measurement. These indices are compared across left-handed and right-handed populations. A few sulci lead to handedness correlated indices. Their instances in one brain chosen randomly are highlighted in this figure, with the list of correlated indices.

identified. It may also be used to guide the inference of new landmarks, either among the branches of the sulci or using another source of information like diffusion-weighted data. Diffusion imaging, indeed, may deeply modify the problem of inter-subject alignment in a near future. This modality may provide new insight into the architectural subdivisions of the brain [26] which should be matched by iconic normalization. This has been shown for instance for the thalamus [49]. It is bound to happen for the cortex, because fiber bundles will lead to architectural parcellations of the cortical surface relatively to the connectivity patterns [39]. Finally, a new morphometry dedicated to the shapes of the bundles will have to be developed.

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